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REVIEW

ANTAZOLINE RENAISSANCE IN THE TREATMENT OF CARDIAC ARRHYTHMIA: A REVIEW

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Abstract: Antazoline is an antihistaminic, immunosuppressive, antiarrhythmic agent. Antazoline can be administered orally, intravenously, intramuscularly or via the ophthalmic route. Antazoline has a limited application as an antiarrhythmic drug. This review was undertaken with the aim to combine the old and the new results of different types of studies (clinical, retrospective, or pharmacokinetic) and sum up the positive and negative effects of antazoline in cardiology and emergency medicine. A literature queries were performed in the following databases: PubMed, Embase, Google Scholar, and Web of Science (all from their inception date till June 2019). The queries covered antazoline in combinations with such terms as antiarrhythmic activity, arrhythmia, electrocardiography, emergency medicine, and cardiology. Additional publications were found by checking all the reference lists. The newest research shows that antazoline may have the highest success rate of pharmacological cardioversion among all drugs used in the contemporary treatment of cardiac arrhythmia (up to 85.3%). The rate of cardioversion with antazoline alone was higher than the combined amiodarone and/or propafenone. Most of the studies which were reviewed indicated that paroxysmal atrial fibrillation, compared to chronic atrial fibrillation, responded more satisfactorily to antazoline treatment. Most patients tolerated antazoline well and conversion was safe, effective, and smooth. Some research proves that antazoline use may also reduce the rate of hospitalization due to the adverse effects. Antazoline has a definite place in the therapeutic repertoire for several cardiac arrhythmias. It should not be neglected as an old drug, and ought to be reconsidered in emergency medicine treatment recommendations.

Keywords: antazoline, atrial fibrillation, cardiac arrhythmia, arrhythmia pharmacological treatment

Antazoline, as an antihistaminic agent, was replaced by newer antihistamines, mostly selective antagonists of the H1 receptor (1). As histamine may play a role in transplant rejection, antazoline's antihistaminic properties may be useful in immunosuppressive therapy (2). In addition, this drug may present antiarrhythmic effects (3). Antazoline can be administered orally, intravenously, intramuscularly or via the ophthalmic route. However, antazoline has had sporadic and limited application as an antiarrhythmic agent (4). Despite the relative lack of published data, antazoline has been marketed in Poland and widely used in cardiology wards and emergency rooms for many years due to its efficacy, safety, and rapid onset of action, within minutes of administration (4, 5). These considerations are especially relevant to the treatment of patients with borderline cardiac compensation (3). Most evaluations reporting on the cardiac effect of antazoline are very old. In the last few years, only six studies have been published that indicate antazoline could be of value in the clinical setting and should not be neglected, as is done at present. There are expectations with regard to both old and new antiarrhythmic drugs, particularly on the efficacy and safety profile (6).

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The aim of this review was to combine both old and new results from different types of studies (clinical, retrospective, or pharmacokinetic), and attempt to sum up the positive and negative effects of antazoline in cardiology and emergency medicine, especially the efficacy of antazoline therapy in various cardiac arrhythmias that are completely different in several studies.

Materials and methods

Four databases – PubMed, Embase, Google Scholar, and Web of Science – covering reports published up to June 2019 were searched with the following keywords and phrases: antazoline, antiarrhythmic activity, arrhythmia, ECG, emergency medicine, and cardiology. The search was limited to English and Polish papers and to the reference lists quoted therein. Additionally, other resources such as Micromedex, Medical Letter, as well as the electronic Stockley Drugs Interaction were searched. Checking the reference lists helped identify other related papers. The selection process was undertaken in parallel by two independent researchers working on each database. The first two authors independently studied all clinical reports. Studies with animals, in vitro studies, and duplicated data were excluded.

RESULTS

After all the materials were collected, a critical review was performed, and the results are presented in this review. Important information on antazoline doses, route of administration, and type of arrhythmias are presented (Table 1).

Mechanism of antazoline action

Antazoline is an H1 receptor antagonist and is, therefore, able to counteract the symptoms of allergic conjunctivitis mediated by histamine (7). Antazoline is a first-generation antihistaminic agent with anticholinergic and quinidine-like properties. The atropine-like action of antazoline is exemplified by the facilitation of A–V conduction, and its quinidine-like action is evidenced in its ability to prolong the refractory period of the atrium (8). The mechanism of action is mediated through interference with membrane permeability to potassium and sodium (9). Antazoline prolongs the duration of the action potential and lowers its amplitude, prolongs the duration of phase 0, reduces the resting potential of phase 4, and reduces the excitability of cardiac tissue (5). Clinically, antazoline lowers the velocity of intra-atrial conduction, prolongs the atrial refractory period, and may improve atrioventricular conduction allowing fast ventricular response to supraventricular arrhythmias (5). According to the Vaughan–Williams classification, antazoline belongs in Class Ia (10).

Pharmacokinetic parameters of antazoline

Pharmacokinetic studies of antazoline are scarce (7). The maximal action of antazoline (iv) is observed after 5 min, and the antiarrhythmic efficacy expires after approximately 1 h (40–60 min) (11). In clinical studies of healthy volunteers, the terminal elimination half-life of antazoline was found to be 2.29 h, with a mean residence time of 3.45 h (12). Intravenous dosage can be repeated safely at intervals of 2–3 h (13).

According to Dreifus et al. (13) the therapeutic efficacy of oral antazoline appears to last for 4–6 h; therefore, the drug (100–200 mg) should be administered 3–4 times daily.

Influence of antazoline on electrocardiographic and hemodynamic parameters

According to Srzednicki et al. (11), antazoline does not affect intraventricular conduction or significantly change the QRS complexes duration; however, an extended prolongation of the QT interval was observed from 10 to 45 s beginning from the 2nd minute after administration of the drug and maintained up to 120 min (end of the observation). QT prolongation may be an important limitation of antazoline (3, 14).

Piotrowski et al. (3) examined the effects of antazoline (administered intravenously in three 100 mg boluses) on hemodynamic and electrocardiographic (ECG) parameters in 10 healthy volunteers. Antazoline caused significant prolongation of the P wave, QRS complex, as well as QT interval, and of the corrected QT interval (QTcF; 101 ± 10 vs. 110 ± 16 ms; 101 ± 12 vs. 107 ± 12 ms; 399 ± 27 vs. 444 ± 23 ms; and 403 ± 21 vs. 448 ± 27 ms, respectively). Additionally, there was a significant decrease in stroke volume (94.9 ± 21.8 vs. 82.4 ± 19.6 mL). A significant correlation was detected between changes in plasma antazoline concentration and changes in cardiac output, heart rate, and diastolic blood pressure. Antazoline slightly impairs hemodynamics, thus significantly reducing stroke volume. The significant prolongation of the P wave and QRS duration corresponds to a drug-induced prolongation of conduction, whereas QT prolongation represents a drug-induced prolongation of repolarization. Farkowski et al. (15) described that prolongation of QTc interval by antazoline, can convert atrial fibril-

Table 1. Antazoline as an antiarrhythmic drug - dose and route of administration and types of arrhythmia treated successfully.

Authors, year, country of study	Patients (total number)	Dose and route of administration	Type of arrhythmias treated with antazoline	Arrhythmias that responded satisfactorily
Kline et al. (19) USA 1962	40	PO Initial dose, 100 mg thrice daily for 3 days The dose was increased to 200 mg 3 or 4 times daily if inadequate response IV 50-800 mg	Premature ventricular systoles Premature atrial systoles Atrial fibrillation Atrial flutter Ventricular tachycardia Paroxysmal atrial tachycardia	Premature atrial systoles Ventricular premature systoles
Dreifus et al. (13) USA 1963	112	PO 400-800 mg daily IV Up to 10 mg/kg	Atrial premature systoles Ventricular premature systoles Paroxysmal atrial tachycardia Paroxysmal nodal tachycardia Atrial flutter Atrial fibrillation Paroxysmal atrial tachycardia with block Accelerated nodal rhythm Ventricular tachycardia	Atrial premature systoles Ventricular tachycardia Multifocal ventricular premature systoles Nonparoxysmal nodal tachycardia due to digitalis excess
Leon-Sotomayor (8) USA 1963	24	IV 100 mg, repeated if required at intervals of approximately 5 min, with the total dose not exceeding 100 mg/kg. IV+PO 200 mg given orally immediately after conversion with intravenous therapy and repeated at 6-hourly intervals	Atrial fibrillation Atrial flutter Paroxysmal atrial tachycardia A-V block and bundle-branch block Atrioventricular dissociation Wolff-Parkinson-White syndrome	Arrhythmias associated with intraventricular conduction defects Partial A-V block and bundle-branch block Arrhythmias associated with digoxin intoxication
Reynolds et al. (17) USA 1964	115	PO and IV 100 mg, 1500 mg	Premature beats (atrial, ventricular, or nodal) Paroxysmal arrhythmias (atrial tachycardia, nodal tachycardia, atrial flutter, atrial fibrillation, or ventricular tachycardia) Prevention of rhythm abnormality	Abolition of ventricular tachycardia and Prevention of paroxysmal atrial tachycardia
Gehring et al. (18) USA 1968	20 case studies	PO 100 mg thrice daily to 200 mg 4 times daily	Atrial fibrillation Atrial flutter Premature ventricular contractions Atrial tachycardia	Atrial fibrillation Atrial flutter Premature ventricular contractions Atrial tachycardia

Table 1. Continued.

Authors, year, country of study	Patients (total number)	Dose and route of administration	Type of arrhythmias treated with antazoline	Arrhythmias that responded satisfactorily
Antani (19) India 1971	50	IV 25 mg/min, dose increased by 100 mg until conversion occurred Maximum 15 mg/kg bw	Paroxysmal atrial tachycardia Paroxysmal nodal tachycardia Atrial fibrillation Atrial flutter Atrial premature beats Ventricular tachycardia Ventricular premature beats	Paroxysmal atrial tachycardia Paroxysmal nodal tachycardia Ventricular tachycardia Ectopic beats (atrial and ventricular)
Shah et al. (9) India 1972	56	IV 50 mg at intervals of 5 min until termination of arrhythmia Maximum 10 mg/kg bw	Atrial ectopic beats Ventricular ectopic beats Paroxysmal supraventricular Tachycardia (atrial and nodal) Atrial fibrillation Ventricular tachycardia	Atrial ectopic beats Ventricular ectopic beats Paroxysmal supraventricular tachycardia (atrial or nodal)
Downar et al. (4) Canada 1975	7	PO and IV Initial 5 mg bolus IV every 5 min up to a maximum dose of 400 mg, followed by a PO maintenance dose of a maximum of 1200 mg/d in divided doses	Severe and debilitating Supraventricular tachyarrhythmia	Paroxysmal supraventricular Tachyarrhythmia Chronic supraventricular Tachyarrhythmia Atrial fibrillation
Srzednicki et al. (11) Poland 1990	43	IV 5 mg/kg bw to a maximum dose of 400 mg	Paroxysmal atrial fibrillation	Paroxysmal atrial fibrillation
Kuch et al. (10) Poland 2000	1325	IV - 100 mg - 200 mg - 300 mg - >300 mg	Paroxysmal atrial fibrillation	Paroxysmal atrial fibrillation
Piotrowski et al. (21) Poland 2014	290	IV 100 mg repeated boluses	Wolff-Parkinson-White syndrome undergoing ablation, sustained atrial fibrillation during procedure	Atrial fibrillation during ablation
Balsam et al. (22) Poland 2015	141	IV 30-50 mg/min until termination of arrhythmia Maximum 500 mg	Atrial fibrillation during procedure of pulmonary veins isolation	Atrial fibrillation during pulmonary vein isolation

Table 1. Continued.

Authors, year, country of study	Patients (total number)	Dose and route of administration	Type of arrhythmias treated with antazoline	Arrhythmias that responded satisfactorily
Maciag et al. (23) Poland 2017	74	IV 50 mg every 5 min up to a total dose of 250 mg	Paroxysmal atrial fibrillation	Paroxysmal atrial fibrillation
Farkowski et al. (24) Poland 2016	432	IV 50 mg every 3-5 min up to a maximum dose of 250-300 mg	Paroxysmal atrial fibrillation	Paroxysmal atrial fibrillation
Wybraniec et al. (26) Poland 2018	180	IV 100 to 200 mg or diluted with a 100-mL solution of 0.9% NaCl	Atrial fibrillation	Atrial fibrillation
Farkowski et al. (15) Poland 2019	14	IV until conversion to sinus or cumulative dose of 300 mg	Atrial fibrillation induced during procedure of pulmonary vein isolation	Atrial fibrillation induced during pulmonary vein isolation

lation to sustained atrial tachycardia or flutter (including 1 : 1 conduction), unmask underlying conduction disturbances or sick sinus syndrome, exacerbate existing heart failure, and provoke chest pain or hypotension.

Bińkowski et al. (14) evaluated the electrophysiological parameters: sinus rhythm cycle length (SRCL), AH, HV, QRS, QT, QTc intervals, Wenckebach point (WP), sinus node recovery period (SNRT), intra- (hRA-CSos) and interatrial conduction time (hRA-CSd), right and left atrium refractory period (RA-; LA-ERP), and atrioventricular node refractory period (AVN-ERP) after successful ablation of supraventricular arrhythmias initially and after 100, 200, and 300 mg of antazoline which was given intravenously to 15 patients. After 100 mg bolus of antazoline, a significant reduction in SRCL was observed. Additionally, antazoline administration caused significant prolongation of HV, QRS, QTc, hRA-CSos, hRA-CSd intervals, RA- and LA-ERP. After a total dose of 300 mg of the drug QT interval prolonged significantly. What is worth to note, the increase of antazoline dose had no impact on AH, Wenckebach point, AVN-ERP, and SNRT.

Side effects of antazoline

Antazoline – as a first-generation H1 antihistaminic – may cause adverse effects; mostly because of poor receptor selectivity. Antazoline may act as an antimuscarinic, anti-alpha-adrenergic, or even anti-serotonergic agent (16).

In general, the side effects of antazoline are seldom serious (e.g., lightheadedness, drowsiness, dizziness). However, nausea, vomiting, dryness, and hiccups can be observed, as well as hypotension, especially when antazoline is rapidly injected. The drug may exhibit or intensify heart failure by imposing a depressive effect on the myocardium – the inotropic negative effect and increase in the peripheral resistance which may result in reduced stroke volume and the cardiac output (11). This drug may induce neurologic effects, such as tremors of the fingers and hands, parkinsonian-like states, hallucination, and grand-mal convulsion (8). Kuch et al. (10) observed mild side effects (6%), of which the most significant was hypotension (1%). A very interesting aspect of the side effects, or even toxic effects, of antazoline therapy was reported in the study of Reynolds et al. (17), who used higher doses of the drug in their study than in any others that we reviewed. Whereas 36% of all of their patients had transient or minimal side effects, 19.4% of patients observed severe effects, including chills and fever,

diarrhea, rashes, and neurologic side effects such as tremor, depression, lightheadedness, muscle spasm of legs, and disorientation (17). Leön-Sotomayor (8) described a patient with chronic atrial fibrillation who became aphasic and developed left-sided hemiparesis 24 h after successful conversion induced by antazoline; however, this patient did not receive anticoagulants before conversion. This effect can be attributed much more likely to peripheral embolism-not drug side effect.

Srzednicki et al. (11) have suggested that in the light of uncommon side effects (6.9%) by administering the dose used in the above study, the drug can be used for outpatient conditions provided that the contraindications are ruled out and the blood pressure is being monitored. Increase of a dose within a range of 250–400 mg increased efficiency of therapy by 20%, yet it resulted in a fivefold increase of drug side effects. In addition, the authors have reported that the correct potassium concentration may determine the efficacy of antazoline. Leön-Sotomayor (8) suggest that potassium undoubtedly increases the effectiveness of antazoline therapy; therefore, the serum levels of this essential element should be determined and deficits, if any, corrected before antazoline administration.

Very high doses of antazoline, approaching 42–50 mg/kg, produced a widening of the QRS complex and decreased myocardial contractility.

Furthermore, Shah et al. (9) found only minimal negative effects during oral antazoline therapy; nausea and vomiting were more frequent when antazoline was taken on an empty stomach. Additionally, drowsiness was observed, particularly when antazoline dose was more than 800 mg/day. Despite the high dose of antazoline used in the study by Downar et al. (4) there were no serious side effects. Some patients reported mild gastrointestinal disturbances, which may be prevented by taking antazoline with food. Additionally, with oral administration, parkinsonian reactions were detected in only two cases and were completely reversed after discontinuation of antazoline treatment (18).

Most of the reports indicated that the side effects of antazoline treatment were few and nondangerous (19); serious and toxic side effects were not encountered (20).

DISCUSSION

Studies reviewed were presented in chronological order.

Kline et al. (20), evaluated the effect of antazoline in 40 patients with premature ventricular systoles, premature atrial systoles, atrial fibrillation, atrial flutter, ventricular tachycardia, and paroxysmal atrial tachycardia. Antazoline was administered orally (32 patients) in an initial dose of 100 mg thrice daily for 3 days. The dose was increased to 200 mg, 3 or 4 times daily if an inadequate response was observed. Eight patients were intravenously administered antazoline (50–800 mg). The drug was effective in minimizing ectopic beats in patients with premature atrial and ventricular systoles. The ectopic concentrations were reduced by 70% or more in all patients (n = 6) with premature systoles. More than 70% reduction in the number of ectopic beats was observed in 19 patients (total number 22) with ventricular premature systoles. Antazoline treatment proved unsuccessful when used in patients with atrial flutter and atrial fibrillation.

Dreifus et al. (13) indicated that antazoline administered intravenously (up to 10 mg/kg; 44 patients) and orally (400–800 mg; 68 patients) caused a transient reduction in cardiac output and stroke volume. Blood pressure was maintained, whereas peripheral vascular resistance increased. Antazoline manifests both – a direct myocardial depressant as well as cholinolytic effects; there was complete suppression of atrial premature systoles in all subjects. Atrial tachycardia that was observed only in the group that received intravenous antazoline was promptly terminated in 80% of patients. Antazoline was ineffective (both orally and intravenously) in the presence of atrial flutter and fibrillation. All patients with frequent ventricular premature systoles had an adequate response to intravenously administered antazoline; however, orally administered antazoline induced a positive effect in 57 of the 61 patients. Ventricular tachycardia was terminated in 6 of 10 patients with intravenous antazoline. Therefore, the authors believe antazoline can be effective in terminating ventricular tachycardia, multifocal ventricular premature systoles, and nonparoxysmal nodal tachycardia due to digitalis excess. However, 1 : 1 conduction resulted in two cases of paroxysmal atrial tachycardia with block engendered by digitalis excess. The authors concluded that antazoline is an effective, well-tolerated antiarrhythmic agent, which may be used in the treatment of ectopic beats of atrial, nodal, or ventricular origin. In deference to the profound myocardial depressant activity of antazoline, it should be administered with caution in patients with reduced cardiac output.

Leön-Sotomayor (8) evaluated, in two schedules, the effect of antazoline in 24 patients with organic heart diseases. In the first model, the dose

was 100 mg antazoline administered intravenously and repeated, if required, at intervals of approximately 5 min, with the total dose not exceeding 100 mg/kg. In the second model, 200 mg antazoline was given orally immediately after conversion with intravenous therapy and repeated at 6-hourly intervals with meals. Antazoline appeared to be effective and safer in arrhythmias associated with intraventricular conduction defects, partially A–V block and bundle branch block; however, in arrhythmias associated with or preceded by a longstanding third-degree heart block, antazoline is contraindicated. The authors indicated that antazoline also showed a high degree of effectiveness against arrhythmias associated with digoxin intoxication.

Reynolds et al. (17) investigated 115 patients with different cardiac arrhythmias (premature beats and paroxysmal arrhythmias) treated with different doses (oral and intravenous) of antazoline (100–1500 mg), depending on the type of abnormal rhythm. Antazoline (100–200 mg; 4 times a day) was also used to prevent paroxysmal atrial flutter (n=6) and paroxysmal atrial fibrillation (n=8), where it was only slightly effective or completely ineffective. In the case of paroxysmal ventricular tachycardia (n = 6), 100 mg antazoline administered 4 times a day was also ineffective; however, when the dose of the drug was increased to 200 mg 4 times a day, the number of attacks reduced significantly. The authors concluded that antazoline seems to be most effective in the abolition of ventricular tachycardia, and is beneficial in the prevention of paroxysmal atrial tachycardia.

Gehring et al. (18) described 20 case studies where antazoline in different doses was used orally in the treatment of patients with various arrhythmias that complicated acute myocardial infarctions and were refractory to other medicines such as quinidine, procainamide, or lidocaine. The authors concluded that atrial fibrillation was successfully converted to normal sinus rhythm with 100 mg antazoline thrice daily to 200 mg four times daily. The authors indicated that this drug has efficacy in atrial flutter, premature ventricular contractions, and atrial tachycardia.

Antani (19) investigated the effect of antazoline on different supraventricular and ventricular cardiac arrhythmia in 50 patients. The drug was administered intravenously at a rate of 25 mg/min. The dose was increased by 100 mg until conversion occurred. The maximum therapeutic dose was 15 mg/kg body weight (bw). This dosage of antazoline converted paroxysmal atrial tachycardia in 93.75% of patients, paroxysmal nodal tachycardia in 75%, ventricular tachycardia in 75%, and atrial fibrillation in more than 50% of cases. Chronic established atrial fibrillation responded less satisfactorily than paroxysmal fibrillation. One case of atrial flutter was treated with antazoline to a good outcome. Additionally, ectopic beats (atrial and ventricular) were rapidly converted by antazoline.

Shah et al. (9) reported the effect of antazoline on 65 arrhythmic episodes in 56 patients. In all cases of ventricular tachycardia, antazoline was administered intravenously (50 mg every 5 min until termination of arrhythmia or a maximum dose of 10 mg/kg bw). In patients with atrial ectopic beats, ventricular ectopic beats, paroxysmal supraventricular tachycardia (atrial and nodal), or atrial fibrillation, 100 mg antazoline was given orally, every 4 h; however, if such a schedule was not effective within 24 h, the dose was increased to 200 mg every 4 h for a further six doses, and, in cases that were not responsive, the dose was further increased to 300 mg every 4 h. The percentage of good response to antazoline treatment was 83.3% in atrial ectopic beats, 87.5% in ventricular ectopic beats, 70.0% and 80.0% in paroxysmal supraventricular tachycardia (atrial or nodal, respectively), and 60% in ventricular tachycardia. In patients with atrial fibrillation, no significant change in the ventricular rate was observed.

Downar et al. (4) investigated seven patients with severe and debilitating chronic or recurrent supraventricular tachyarrhythmia. Antazoline was used because conventional antiarrhythmic therapy (e.g., quinidine, procainamide, digoxin, propranolol) failed. An initial intravenous administration of a 5 mg bolus of antazoline was given every 5 min up to a maximum dose of 400 mg, followed by an oral maintenance dose of a maximum of 1200 mg/day in divided doses. Antazoline has been recommended for the treatment of patients with paroxysmal or chronic supraventricular tachyarrhythmia and atrial fibrillation.

Srzednicki et al. (11) evaluated the effect of antazoline (5 mg/kg bw to a maximal dose of 400 mg) in a group of 43 patients, most of whom (35 patients) suffered from paroxysmal atrial fibrillation. The drug was administered iv at a rate of 50 mg/min during the first 2 min, then at 25 mg/min for between 3 and 6 min, and at 12.5 mg/min between 7 and 22 min. This study demonstrated that the mean efficient dose of antazoline is 2.8 ± 0.2 mg/kg bw, whereas the mean time from administration of the drug to the restoration of the sinus rhythm is 7.3 ± 0.9 min.

Kuch et al. (10) investigated the effect of intravenous antazoline in converting paroxysmal atrial

fibrillation to sinus rhythm in a large group (n = 1325) of patients with paroxysmal atrial fibrillation who were treated with antazoline in different doses. Their study was a retrospective analysis where patients were divided into four groups based on the total dose of antazoline required to restore sinus rhythm. The patients in those four groups received 100, 200, 300, and >300 mg intravenous antazoline, respectively. According to the antazoline dose, the authors evaluated the efficacy of antazoline as 46%, 54.5%, 50%, and 20.5% for the lowest and the highest dose, respectively. Moreover, the authors evaluated the efficacy of therapy in relation to the selection of antazoline as the first, second, and third drug for conversion, and found significant differences in the effectiveness of the antiarrhythmic procedure – 54.5%, 54.7%, and 46.1%, respectively. Additionally, no differences in therapeutic efficacy was observed in relation to sex (53% for females; 51.4% for males) and age (<40, 53.7%; 40–65, 53.3%; and >65, 48.6%). The authors inferred that antazoline therapy was relatively safe within the dose range from 100 to 300 mg, and they recommended antazoline in paroxysmal AF as the first-line drug when a ventricular rhythm is <100 beats/min, and as the second drug when ventricular rhythm increased 100 beats/min after the usage of drug which decreased heart rate.

Piotrowski et al. (21) examined 290 patients with Wolff-Parkinson-White syndrome undergoing ablation; during this procedure, 12 patients developed sustained atrial fibrillation, which did not stop for 10 min. In this group of patients, 100 mg antazoline in repeated boluses was used successfully, and sinus rhythm was restored after a 425 ± 325 seconds. The authors indicated that antazoline during atrial fibrillation slightly prolonged RR intervals as well as reduced the percentage of fully pre-excited QRS complexes. Antazoline gradually increases A–A intervals during atrial fibrillation, converting it into more organized atrial activity (atrial flutter/tachycardia) before resumption of sinus rhythm. The authors concluded that antazoline safely and rapidly coverts atrial fibrillation during ablation of accessory pathways; moreover, antazoline did not completely block the accessory pathways, and ablation may be continued.

Balsam et al. (22) evaluated in retrospective, non-randomized, no placebo-controlled study the effect of antazoline for termination of atrial fibrillation in 141 patients (67 with paroxysmal and 74 with persistent atrial fibrillation) undergoing pulmonary vein isolation. Antazoline was administered iv (30-50 mg/min) until sinus rhythm was restored and this therapy was effective in 56% of patients (in a group of patients with paroxysmal atrial fibrillation this ratio reached 90.9%). Less than one-third of persistent atrial fibrillation cases was restored after such treatment.

One of the best studies associated with antazoline use in cardiac arrhythmias was conducted by Farkowski et al. (5). It was a randomized, double-blind, placebo-controlled study of the clinical efficacy of antazoline in rapid cardioversion of paroxysmal atrial fibrillation (The AnPAF Study). In 2017 the results of this first randomized controlled trial with 74 patients with atrial fibrillation episodes lasting less than 43 h were published (23). 36 patients were treated with antazoline (50 mg diluted to 10 mL every 5 min up to a total dose of 250 mg – 50 mL. The control group (38 patients) received 0.9% saline in boluses of 10 mL every 5 min up to a maximum volume of 50 mL. During observation lasted 1.5 h, the successful conversion of paroxysmal atrial fibrillation was achieved in 72.2% of patients received antazoline and in 10.5% cases in the control group. The median time to restore sinus rhythm after antazoline administration was 16 min. Farkowski et al. (24) assessed the comparative effectiveness and safety of antazoline and propafenone-based strategies in the pharmacological cardioversion of short-duration atrial fibrillation. In total, 432 cases of cardioversion were analyzed. Antazoline was administered 334 times, and propafenone 98 times. Antazoline was administered at a dose of 50 mg every 3 to 5 min up to a maximum dose of 250–300 mg or until conversion to sinus rhythm, whereas all patients in the propafenone group received a fixed dose of 70 mg propafenone. Cardioversion with antazoline or propafenone was successful in 71.6% and 55.1% of patients, respectively. The rate of hospitalization due to the adverse effects of the treatment was low and similar in the study groups: 3.0% for antazoline and 4.1% for propafenone.

Farkowski et al. (25) assessed also the effectiveness and safety of antazoline-based therapy in patients with a stable coronary artery disease undergoing pharmacological cardioversion of short-duration AF in the emergency department (retrospective case-control study, 2008-2012). Antazoline was administered 334 times (138 patients with stable coronary artery disease – CAD; 196 the control group). Patients in the CAD group were older and with a history of myocardial infarction (65 patients). In CAD group, the antazoline effectiveness was significantly higher (82.6% vs 63.8%). Authors indicated that in selected patients even with a history of

myocardial infarction, antazoline-based cardioversion of short-duration atrial fibrillation can be an effective and safe choice.

Wybraniec et al. (26) evaluated the success rate and safety of pharmacological cardioversion of atrial fibrillation with intravenous antazoline (CANT study (Cardioversion With Antazoline Mesylate)). Antazoline was administered either as a single or repeated slow (3-minute) undiluted intravenous bolus of 100 to 200 mg or diluted with a 100-mL solution of 0.9% NaCl and infused over 5 to 15 min. 180 patients with short-duration atrial fibrillation received antazoline alone (n = 109) or in combination with propafenone and/or amiodarone (n = 71), respectively. Antazoline had the highest success rate of pharmacological cardioversion among all drugs (85.3%) and it was comparable with propafenone and higher than amiodarone treatment. The rate of cardioversion with antazoline alone was higher than the combined amiodarone and/or propafenone.

Farkowski et al. (15) assessed the influence of antazoline on atrio-venous conduction and other electrophysiological parameters in patients (n = 14, mean CHA_2DS_2-VASc score 1.6) undergoing pulmonary vein isolation. Antazoline was administered intravenously in a mean dose of 257.1 mg. Pulmonary vein potentials and atrial capture during pulmonary vein stimulation were present before and after the administration of antazoline. Wenckebach point and atrial conduction times did not change, but the atrioventricular node effective refractory period improved significantly (324.7 ± 84.5 ms vs 284.3 ± 48.6 ms). The drug was effective in all 5 (100%) cases of AF induction during the electrophysiological study and no serious adverse events were observed. The mean time to conversion was 8.4 ± 6.2 min. Authors indicated that antazoline may be useful for pharmacological cardioversion of AF occurring during AF ablation because of the lack of influence on atrio-venous conduction and high clinical effectiveness.

Limitation of reviewed studies

Successful or harmful antiarrhythmic intervention in various types of arrhythmia was observed in the papers reviewed. It is very difficult to present a strong recommendation for the treatment of arrhythmia based on the studies in this review. Most of the studies were not randomized. In particular, the number of patients in the oldest evaluation was not sufficient to generate strong evidence, and the drug was administered orally. The most important reason for the different effects of antazoline therapy observed between these studies may be the classification of patients with regard to the therapy. In many studies, patients with chronic AF were treated with antazoline. The second reason could be the route of administration, which may have a significant effect on the therapy and, finally, most of the old studies (4, 18) were conducted with small numbers of patients. The biggest group of patients were evaluated in Polish studies: Kuch et al. (10) (n = 1325), Farkowski et al. (23) (n = 432), and Piotrowski et al. (21) (n = 290). Multicenter randomized studies are urgently required in this area, especially for off-label (according to the Food and Drug Administration recommendations) treatment of cardiac dysrhythmias (27). Using antazoline in the prevention (orally administration) of arrhythmias is not recommended, especially because of the need for frequent dosing and very low availability of the oral antazoline formulation.

Pharmacological cardioversion of atrial fibrillation – treatment based on 2016 European Society of Cardiology Guidelines

Even if electrical cardioversion seems to restore sinus rhythm quicker and more effectively in short term (28), the initial treatment of a stable patient with atrial fibrillation based on pharmacological cardioversion is more often, especially in pre-hospital treatment and emergency departments. Pharmacological cardioversion does not require sedation or fasting, antiarrhythmic drugs are widely available in different levels of medical care. In selected patients with infrequent symptomatic episodes of paroxysmal atrial fibrillation, drugs (flecainide or propafenone) can be even self-administrated by themselves at home (‘pill in the pocket’ therapy) (29). Pharmacological cardioversion restores sinus rhythm in approximately 50% of patients with recent-onset atrial fibrillation (28). If the patient is unstable and deteriorating, with any of the adverse signs and symptoms (syncope, shock, heart failure, myocardial ischemia), synchronized electrical cardioversion is immediately required.

In 2016, the European Society of Cardiology published the guidelines for the management of atrial fibrillation which were produced after careful consideration of the scientific and medical knowledge and the evidence available the time of their publication. The antazoline is not mentioned in this document as a possible way of treatment. The detailed guidelines concerning antiarrhythmic drugs for the acute restoration of sinus rhythm are presented in Table 2.

Table 2. 2016 European Society of Cardiology Guidelines for the management of atrial fibrillation - antiarrhythmic drugs used for pharmacological cardioversion.

Drug	Route	Ist dose	Follow-up dose	Risks
Flecainide	Oral IV	200-300 mg 1.5-2 mg/kg over 10 min	N/A	Hypotension, atrial flutter with 1:1 conduction, QT prolongation. Avoid in patients with IHD and/or structural heart disease.
Amiodarone	IV change to oral route within 24 h of iv administration	5-7 mg/kg over 1-2 h	50 mg/h to a maximum of 1.0 g over 24 h	Phlebitis, hypotension, bradycardia/ AV block. Will slow ventricular rate. Delayed conversion to sinus rhythm (8-12 h).
Propafenone	IV Oral	1.5-2 mg/kg 450-600 mg	N/A	Hypotension, atrial flutter with 1:1 conduction, QRS prolongation (mild). Avoid in patients with IHD and/or structural heart disease.
Ibutilide	IV	1 mg over 10 min	1 mg over 10 min after waiting for 10 min	QT prolongation, polymorphic ventricular tachycardia/ torsades de pointes (3-4% patients). Will slow ventricular rate. Avoid in patients with QT prolongation, hypokalemia, severe LVH or low ejection fraction.
Vernakalant	IV	3 mg/kg over 10 min	2 mg/kg over 10 min after waiting for 15 min	Hypotension, non-sustained ventricular arrhythmias, QT and QRS prolongation. Avoid in patients with SBP <100 mm Hg, recent (<30 days) ACS, NYHA Class III and IV heart failure, QT interval prolongation (uncorrected QT. 440ms) and severe aortic stenosis

The above table was prepared according to the 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS.
ACS - acute coronary syndromes; AV - atrioventricular; EACTS - European Association for Cardio-Thoracic Surgery; ESC - European Society of Cardiology; IHD - ischaemic heart disease; IV - intravenous; LVH - left ventricular hypertrophy; N/A - not applicable; NYHA - New York Heart Association; SBP - systolic blood pressure.

CONCLUSIONS

After careful consideration of the available studies concerning the use of antazoline as an antiarrhythmic drug, we emphasize the following points:

- Most of the studies indicated that chronic atrial fibrillation responded less satisfactorily to antazoline treatment than paroxysmal atrial fibrillation.
- Most of the patients tolerated antazoline well, and conversion was safe, effective, and smooth.
- In the case of myocardial infarction and myocarditis – because myocardial repolarization is decreased, antazoline can cause hypotension, accelerate atrioventricular conductions, and increase the ventricular response.
- Antazoline use is contraindicated in advanced second- and third-degree heart block, and in severe underlying cardiac disorders which are defined as heart failure.
- Antazoline should be administered intravenously under continuous cardiac monitoring in the setting of emergency department, or cardiac intensive care unit.

Antazoline has a definite place in several therapeutic interventions for cardiac arrhythmia. This drug has an effect on electrophysiological parameters of the atrial muscle and has a rapid onset of action. No significant negative effect on sinus node function and atrioventricular conduction in a unique property among antiarrhythmic drugs (14). The antazoline should not be neglected as an old drug, and ought to be reconsidered in emergency medicine treatment recommendations.

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Conflicts of interest

The authors declare no conflict of interest.

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